CHAPTER 87

Topical Medications

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BASIC INFORMATION

Topical medications (Table 87-1) are applied directly on the painful body area, where they penetrate the skin. A topical medication's site of activity is in the peripheral tissues, including soft tissue and peripheral nerve, directly underlying the site of application. Topical drugs, formulated as a gel, cream, liquid, or patch, should not produce any clinically significant systemic drug concentration.

Transdermal medications, on the other hand, are also applied directly to the skin, but the site of drug application can be distant from the area of pain (currently available transdermal drugs include fentanyl and clonidine). Transdermal drugs' sites of activity are not local but via a systemic effect. The medication of transdermal delivery systems is typically contained in a pooled reservoir within a patch, which is designed to push drug directly into the bloodstream. Therefore, unlike topical medication patches, a transdermal patch cannot be cut into different sizes.

Therefore, the key difference between topical and transdermal drug delivery systems is that a topical medication does not result in any clinically meaningful blood levels, whereas a transdermal drug must result in clinically effective serum concentrations for its clinical effect.

History

Applying medicinal substances directly on the skin is likely one of the oldest routes of administration. Ancient cultures ground herbs and plants into pastes for medical uses, including the treatment of pain. Over the past century, many tonics, gels, salves, and lotions have been sold as over-the-counter remedies for pain, although most have little to no scientific study to back their claims (e.g., "snake oils"). Many of these older topical medicinal products may in fact act only as counterirritants—that is, they produce a mild to moderate noxious stimulus that then suppresses the perception of the pain.

Only in the past few decades has the pharmaceutical industry begun to develop topical drugs for the treatment of pain with the aim of producing products with proven efficacy. However, even at the time of this writing, the commercial availability of topical pain medication with controlled clinical trial evidence of efficacy remains sparse. Yet, much development and clinical trial study are currently under way, with the promise of safe and effective topical drugs for the treatment of many acute and chronic painful conditions.

Theoretical Bases

Mechanisms of Action

Because topical drugs, by definition, must act locally on dysfunctional or damaged soft tissues or peripheral nerves, all abnormal pathophysiologic events within the periphery that generate or maintain pain are potential targets for these medications. In acute pain syndromes and arthritic conditions, topical drugs may play a role in reducing the inflammatory response and concurrent sensitization of nociceptors. In chronic neuropathic pain, abnormal neuronal activity abnormal impulse generation secondary t sodium channels or α-adrenergic receptors is a p as is the ongoing neurogenic inflammatory resp

Clinical Advantages

Theoretically, topical drugs' activity should b of pain generation, unlike oral and other systemic need to enter the bloodstream before they arrive site of action. Therefore, because topical drugs any clinically significant serum levels, adverse re ited to those produced by local reaction, such as rash. Most of the currently prescribed oral and tr ications for pain, both acute and chronic, are ha systemic side effects. With nontopical agents, it is essary to titrate the dosage to effect, either pain r ble side effect; unfortunately, the latter often oc an aborted drug trial and the patient still sufferir

Another advantage to topical agents is the drug interactions, again due to their lack of s The potential for drug-drug interactions is co patients with chronic painful conditions, such with arthritis or postherpetic neuralgia (PHN) fering from painful neuropathies, such as diab immunodeficiency virus (HIV) patients.

When treating chronic pain conditions, trea agents requires slowly titrating the dose until pain relief or intolerable side effects are reported time-consuming procedure that may take weeks The time to a noted effect with topical agents, o usually is on the order of days. Thus, yet anot topical drugs is the significant amount of time sa to titrate the dose over several weeks or more.

An additional important advantage of topi ease of use. Patients either need to apply a liqu several times a day or, with some preparation once or twice a day.

Clinical Information

Indicated Pain Conditions. Clinical cond with pain in which a topical agent may have include both acute and chronic pain states. Acu suitable for topical pharmacotherapeutic int acute soft tissue injuries (e.g., sprains, strains, postsurgical pain, and acute herpes zoster (s nonmalignant pain states appropriate for topic include arthritic conditions and chronic perip pain conditions, such as PHN, diabetic poly neuropathy, idiopathic neuropathy, complex r dromes, stump pain, and other neuroma pains.

Medication Classes. Currently only a fe mercially available for the treatment of pain, in dal antiinflammatory agents, capsaicin, and loca However, several new topical drugs—using di

BLE 87-1. Topical versus transdermal drug delivery

	Topical	Transdermal
tion site	Skin: directly on painful skin	Skin: distant from painful region
ctivity	Peripherally (soft tissue, nerve)	Systemically
lrug concentration	Insignificant	Necessary
c side effects	No	Yes
ı needed	No	Yes
ug interaction	No	Yes

ns, with a new active medication ingredient, or both—are being investigated (at the time of this writing), and it is hat they will prove efficacious in the not too distant future reatment of a variety of acute and chronic pain conditions. eral different topical formulations may be available the same medication class, which may differ signifi- with regard to efficacy and side effect profile. Such dif- topical drugs in the same class may differ in several ly significant ways, including (a) the actual active medi- being delivered: (b) the topical vehicle formulation's ents, which affect skin penetration and drug delivery; the application form in which the drug is available, such d, gel, salve, or patch/plaster. Each of these three factors tly important relevance with regard to the topical drug's and adverse events (Table 87-2).

GS

eroidal Antiinflammatory Drugs

ll of the drug classes, the nonsteroidal antiinflammatory NSAID) class has the most studied and currently avail- able different topical drug formulations that are commercially available or under investigation. Many different NSAIDs with vastly different vehicle formulations have been assessed in mostly acute pain syndromes and arthritic conditions.

Mechanism of Action

NSAIDs traditionally have been thought to have their primary mechanism of analgesic activity in the periphery, specifically via their inhibition of prostaglandin synthesis. However, a dissociation between the degree of pain relief of certain NSAIDs and their actual antiinflammatory effects suggests other important analgesic mechanisms of activity (1), including other peripheral effects, such as inhibition of the lipoxygenase pathway, inhibition of excitatory amino acids, and effects on G protein–mediated signal transduction (2).

Topical NSAIDs may also have direct effects on damaged and dysfunctional peripheral nerves. Topical NSAIDs theoretically could reduce primary afferent sensitization occurring as part of a localized abnormal neurogenic inflammatory response (3). An animal study of rabbit corneal nerve injury reported a significant reduction of abnormal neural activity and mechanosensitivity after application of topical diclofenac (4).

Clinical Trial Data

Acute Pain. Topical NSAID treatment has been studied for several clinical conditions associated with acute pain, including minor sports injury pain, postsurgical pain, and ophthalmic pain. A multicenter, randomized, double-blind, placebo-controlled study of acute sports injury pain found significant reductions of pain over a 2-week period with a diclofenac patch/plaster (5). An open-label study observed a 60% reduction in pain with this diclofenac patch/plaster in traumatic sport and overload injuries (6). Similar controlled studies in acute soft tissue injuries revealed significant reductions in pain over the first 48 hours with an ibuprofen cream (7) and over 7

TABLE 87-2. Controlled and uncontrolled studies assessing the efficacy of topical drugs for the treatment of pain

		Arthritic pain (c/uc)		Acute pain (c/uc)		Neuropathic pain (c/uc)		
g class	Agent	Rheumatoid arthritis	Osteoarthritis	Soft tissue	Postsurgical	Acute herpes zoster	Postherpetic neuralgia	Diabetic neuropathy
	Diclofenac patch/ plaster		+/	+/+				
	Diclofenac gel			/+				
	Diclofenac with hyaluronan		+/					
	Diclofenac with ether					+/+*	+/+*	
	Ibuprofen cream			–/				
	Ketoprofen gel			+/+				
	Piroxicam gel							
	Eltenac gel		+/		+/			
	Aspirin/ether		+/		+/	+/+*	+/+*	
esthetic	Lidocaine							
	Lidoderm patch						+/+	–/+
	Lidoderm gel						+/+	–/+
	Lidocaine/prilocaine							
	EMLA cream			+/**			–/	
	EMLA patch			+/**				
n		M/	+/		+/		M/M	M/M
ie	Gel				+/		/+	/+

ontrolled study(ies); EMLA, eutectic mixture of local anesthetics; M, mixed results; NSAIDs, nonsteroidal antiinflammatory drugs; uc, uncontrolled study(ies) dotal report(s); +, positive results; –, negative results; *, single-session studies; **, pain associated with venipuncture, biopsy, and circumcision.

days with ketoprofen gel (8). An open-label uncontrolled study comparing several different topical gels for acute soft tissue injury pain observed that diclofenac gel and ketoprofen gel were similar in efficacy, whereas piroxicam gel was less effective (9).

A double-blind comparative study assessed piroxicam gel applied preoperatively to patients undergoing an inguinal repair, local anesthetic inguinal block, and no treatment and reported that both the topical NSAID gel and the nerve block similarly reduced pain scores, time to first analgesic, and total opiate consumption as compared to the no-treatment group (10). Double-blind controlled studies have assessed topical NSAIDs for the treatment of acute pain associated with traumatic corneal abrasions and found significant reductions in pain (10–12). A study has also reported significant pain reduction with topical diclofenac treatment for postoperative pain associated with phototherapeutic keratectomy (13).

Arthritic Pain. A large randomized, multicenter, double-blind, 4-week study compared topical eltenac gel with oral diclofenac and placebo in patients with osteoarthritis of the knee and found that both active treatments were significantly better than placebo in reducing pain only in patients with severe symptoms, but that the number of gastrointestinal adverse reactions were three times higher in the oral NSAID group as compared to the topical NSAID group (14). Controlled studies demonstrated efficacy of a topical diclofenac in hyaluronan for the treatment of osteoarthritis (15–17). Placebo-controlled studies have reported significant reductions in pain with topical diclofenac plaster (patch) in patients with osteoarthritis of the knee (18), and inflammatory peri- and extraarticular rheumatologic diseases (19). After several days of diclofenac plaster application in patients with monolateral knee joint effusion, low levels of diclofenac were measurable in the synovial fluid without producing elevated serum levels (20). An open-label uncontrolled study reported topical flurbiprofen patches provided significantly better pain control as compared to oral diclofenac with significantly fewer gastrointestinal side effects after 2 weeks of treatment in patients with "soft-tissue rheumatism" (21).

Neuropathic Pain. A single-session, double-blind, crossover study reported significant pain reduction for the treatment of both acute herpes zoster and PHN with a topical diclofenac/diethyl ether mixture with no significant side effects (22). This same study reported that an indomethacin/diethyl ether topical mixture was not superior to placebo in a single-session protocol. Another single-session study observed significant pain reduction in patients suffering from PHN with hydrous stupes (topical patches) containing indomethacin, ketoprofen, or flurbiprofen (23). However, no long-term efficacy studies with topical NSAIDs have been published for the treatment of either acute herpes zoster or PHN. No studies have assessed the use of topical NSAIDs for other peripheral neuropathic pain conditions.

Aspirin

Although no commercially produced form of topical aspirin is available at the time of this writing, several studies have reported the results of compounded formulations of topical aspirin for the treatment of pain associated with herpes zoster.

Mechanism of Action

Like the topical NSAIDs, topical aspirin may alleviate pain by affecting the inflammatory response and, at least theoretically, in neuropathic pain states by reducing neurogenic inflammation.

Neuropathic Pain

A double-blind, placebo-controlled, single-session clinical [illegible] statistically significant pain relief in patients with acute herpes zoster and PHN after application of a topic aspirin/diethyl mixture (24). In addition, several open-lab studies have described pain reduction in PHN using topic mixtures of aspirin and chloroform or diethyl ether (25,26). N controlled study has assessed the long-term benefits and sic effects with topical aspirin formulations.

Local Anesthetics

Over the past decade, two commercially produced forms topical local anesthetics have extensively undergone the rigors placebo-controlled clinical trials testing, Lidoderm gel ar patches and EMLA (eutectic mixture of local anesthetics, 2.5 lidocaine and 2.5% prilocaine) cream and patch. To date, bc products have proven efficacy for different clinical pain stat Lidoderm for peripheral neuropathic pains and EMLA for act pains associated with invasive procedures, such as venipunctu Other topical formulations of local anesthetics have also bc reported for the treatment of acute pain states.

Mechanism of Action

Local anesthetic drugs applied topically are thought to p vide pain relief by reducing ectopic discharges in superfi somatic nerves, which are damaged and dysfunctional in r ropathic pain states and are normally active in acute inju such as venipuncture. It is not necessary to produce a ' anesthesia of the skin to produce clinically significant relief in chronic neuropathic pain states. Animal models of ropathic pain have shown significant reductions in the at mal tonic, evoked, and ectopic activity in damaged perip nerve with local anesthetic concentrations dramatically b that which blocks impulse conduction (27,28). In additi topical patch, such as the Lidoderm patch, has been sho have an added benefit of protecting allodynic skin from mechanical stimulation and thereby of reducing an allo patient's pain (29,30).

Neuropathic Pain

A large multicenter, placebo-controlled, double-blind reported significant pain relief with 4 weeks of lidocaine (Lidoderm) use in patients with long-standing PHI mechanical allodynia (30). Another controlled trial in using an enriched enrollment crossover design, demon that long-term lidocaine patch users (mean duration o use was 3.3 years; mean duration of PHN 7.3 years) pr the lidocaine patch to the placebo patch, 78% versus 9% ((31). In addition, several double-blind, placebo-controll gle-session studies have reported Lidoderm, both the patch formulations, to be effective in significantly redu pain of PHN without any significant side effects Lidocaine serum levels after use of this gel and the p mulation are an order of magnitude below antiarr serum levels and are thus very safe, even in patients diac conditions (29,30,33).

A randomized controlled trial of topical lidocaine patches for the treatment of painful diabetic ne showed clinically significant reductions in pain with active and placebo treatments in the vast majority o but no statistical difference between the two treatme BS, Gianis A, *unpublished results*, 1988). Of interest majority of subjects in this study continue to use the patch or gel in a compassionate use protocol with meaningful reductions in pain, even if they respon placebo treatment in the controlled study. Anecdota also suggests this drug may be useful for the treatme peripheral neuropathic pains, such as idiopathic po thy, painful mononeuropathy, stump pain, reflex s dystrophy, and painful HIV neuropathy (35,36).

Long-term efficacy appears to be maintained for this new ›pical lidocaine preparation. PHN and diabetic neuropathy atients who have applied Lidoderm for several years report ›ntinued pain relief, with some patients noticing a decrease in ıe size of the painful region and others needing to apply the ›pical medication less and less frequently. No significant acute ·chronic side effects have been observed.

The other commercially available formulation of topical :al anesthetic, EMLA, has failed to demonstrate efficacy supe›r to placebo (37).

:ute Pain

Controlled studies have reported EMLA cream applied ıder an occlusive dressing for 60 minutes reduces pain associ›d with venipuncture (38,39), intramuscular saline injections)), spinal needle insertion (41), excisional biopsy or curettage th electrosurgery of cutaneous lesions (42), and pain from cirmcision in neonates (43). A patch impregnated with EMLA ıs also shown to reduce pain associated with a skin biopsy in ldren (44) and venipuncture pain in adults (45).

A controlled comparative study of volunteers undergoing ravenous catheterization reported that liposome-encapsu›d tetracaine provided more effective pain relief than EMLA am after 60 minutes' application time, although the tetrane also caused more erythema than the EMLA (46). Topical ›paracaine was shown in a double-blind study to reduce the n after photorefractive keratectomy (47). A double-blind dy reported equally effective pain reduction with the use of ical bupivacaine-adrenaline-cocaine and topical tetracaine-enaline-cocaine mixtures for pain associated with wound ıring (48). A double-blind study assessed the efficacy of topilocal anesthetics for pain associated with suturing lacerations hildren and concluded that topical prilocaine-phenylephrine ; tetracaine-phenylephrine (tetraphen) was as effective as cal tetracaine-adrenaline-cocaine (49).

›saicin

:hanism of Action

'apsaicin is an over-the-counter drug composed of an ıct of chili peppers. It has been postulated that capsaicin :tively stimulates and then depletes substance P from nociive primary afferents and thus may produce pain relief in ıin chronic pain states. However, this physiologic activity ıot been definitively proved to be the mechanism of action ırrently available capsaicin products. An animal study of rimental polyarthritis has noted that pretreatment with ıicin significantly attenuated joint swelling and radiologic histologic measures of arthritic changes, suggesting that ıicin may directly suppress inflammation (50). Moreover, ıicin produces a counterirritant effect in a majority of nts by causing a mild to severe burning on application, ı may also be a potential therapeutic pain mechanism. use of this commonly occurring burning on application, bo-controlled trials of capsaicin should be interpreted caution since both subject and researcher are unblinded this occurs.)

›pathic Pain

›ical capsaicin has been studied in PHN and painful dianeuropathy with mixed results. In PHN, several studies reported reductions in pain (51–54), whereas others have ½). Similarly, controlled studies in painful diabetic neuropave also resulted in both negative and positive findings. A mized controlled trial of 0.075% capsaicin in painful dianeuropathy showed no benefit (55). Another controlled using 0.075% capsaicin in painful diabetic neuropathy reported improvement in pain with capsaicin, although an intent-to-treat analysis was not performed (56). A controlled trial using an active placebo (a topical substance that also produced burning on application but had no pain-relieving capabilities) reported no difference between capsaicin and this active placebo in patients with a variety of painful polyneuropathies (57). One small controlled study reported topical capsaicin reduced the pain of postmastectomy syndrome (58).

Unfortunately, currently available formulations of capsaicin have been disappointing clinically as an analgesic agent for all neuropathic pains (59). Currently, most authorities rarely prescribe the drug for the treatment of neuropathic pain due to its overall poor efficacy and the high proportion of patients who complain of a worsening of their pain with drug application.

Arthritis Pain

Two controlled studies have demonstrated efficacy and safety for the use of topical capsaicin in the treatment of arthritis pain. A small double-blind, placebo-controlled study concluded that capsaicin significantly reduced hand pain from osteoarthritis but not pain from rheumatoid arthritis (60). However, a large double-blind study of arthritic knee pain reported significant pain relief in both rheumatoid arthritis and osteoarthritis, with more relief reported by rheumatoid arthritis subjects (61).

Clonidine

At the time of writing, no topical clonidine product is commercially available. However, a new formulation of a topical clonidine gel is being studied for a variety of neuropathic pain states.

Mechanism of Action

Clonidine is an α_2-adrenergic partial agonist. Alpha-2 receptors are autoreceptors located on the sympathetic nerves' terminals, which when activated inhibit their release of norepinephrine. Several lines of evidence suggest an abnormal adrenergic sensitivity in peripheral neuropathic pain states. For instance, locally infused adrenaline results in a worsening of pain and allodynia patients with reflex sympathetic dystrophy (62) and PHN (63). In addition, animal models of peripheral neuropathic pain have shown that injured neurons are sensitive to adrenergic activity, that is, an increase in ectopic impulse generation occurs in response to sympathetic agonists and to activation of postganglionic sympathetic efferent axons (64). Moreover, this adrenosensitivity appears to be an inherent property of the injured somatic peripheral nerve (65). Thus, application of clonidine topically may reduce release of norepinephrine from sympathetic nerve terminals, thereby alleviating the abnormal ectopic firing resulting from the dysfunctional nerve's adrenosensitivity, and, at least theoretically, result in clinically meaningful reductions in pain and allodynia.

Neuropathic Pains

No controlled studies have been performed using a topical form of clonidine, at the time of this writing. However, uncontrolled pilot studies have been performed assessing different concentrations of this new formulation of topical clonidine gel for the treatment of PHN, complex regional pain syndrome type I, and painful diabetic neuropathy. These open-label studies have observed improvement in pain and hyperalgesia in some patients (66). Controlled trials with topical clonidine gel are being planned.

One uncontrolled case series assessed the efficacy of transdermal clonidine patch (Catapres) in four patients with "sympathetically maintained pain" and two with "sympathetically independent pain" (67). This series observed that the patients with sympathetically maintained pain obtained complete relief

of hyperalgesia only in the localized skin region under the patch but no change in the spontaneous ongoing pain, whereas no pain relief at all was noted by the two patients with sympathetically independent pain.

CONCLUSIONS

Theoretically, topical drugs have many clinically relevant advantages over other pharmacotherapeutic drug delivery systems, such as oral, transdermal, and intrathecally delivered drugs. By applying a drug directly to the skin, where it penetrates and acts directly at a site of pain generation without the need for systemic activity or invasive procedure, topical medications have the promise of producing pain relief with few side effects and little risk and cost. In the past, the question plaguing topical drug delivery has been whether clinically meaningful degrees of pain relief can be achieved with topical administration. Controlled clinical trials have demonstrated efficacy for a variety of topical drugs and topical formulations, such as NSAIDs, in topical treatment of acute soft tissue injury and arthritis and neuropathic pain. Anesthetics' treatment of chronic peripheral neuropathies. The treatment of acute pain associated with invasive procedures looks bright for topical drug delivery, with many newer agents being studied for the treatment of both acute and chronic pain conditions. Because of their efficacy, safety, quick time of onset, and ease of use, topical medications should be considered first-line agents for the treatment of many pain states.

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